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HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

DEC 13 1995

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: **ORTHOPHENYLPHENOL** - Review of a carcinogenicity study in the mouse, submitted under Section 6(a)(2) of FIFRA. EPA DP Barcode D212562; EPA Submission No. S482630; EPA MRID# 43545501; EPA Pesticide Chemical Codes 064103(OPP)/064104 (SOPP), Caswell No.s 623AA(OPP)/787(SOPP); Reregistration Case# 2575.

TO: Kathryn Davis/Ron Kendall, PM 52
SRRD (7508W)

FROM: Stephen C. Dapson, Ph.D. Stephen C. Dapson 12/21/95
Senior Pharmacologist, Review Section I
Toxicology Branch II/HED (7509C)

THRU: Yiannakis M. Ioannou, Ph.D., D.A.B.T. Y. M. Ioannou 12/11/95
Section Head, Review Section I
and
Stephanie R. Irene, Ph.D. Stephanie R. Irene 12/11/95
Acting Chief, Toxicology Branch II

Health Effects Division (7509C)

Action Requested: Review a carcinogenicity study in the mouse with Orthophenylphenol.

Recommendations: TBII reviewed the carcinogenicity study in the mouse with Orthophenylphenol submitted by the registrant in support of reregistration. The following is the summary from the review:

In a carcinogenicity study (MRID# 43545501) B6C3F1 albino mice (50/sex/dose group) from Charles River Laboratory, Portage, MI received ORTHO-PHENYLPHENOL (99.88% a.i.; Lot# 8800005-24, mixture of Dow Chemical Company and Miles, Inc. products) in the diet for 24 months at dose levels of 0, 250, 500 and 1000 mg/kg/day. A satellite group of ten animals/sex/dose group were sacrificed at 12 months.

Systemic toxicity was noted in treated females at 3 months as decreased body weight gain (10-12%), statistically significant but

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not dose related. At 12 and 24 months there was a 14-25% decrease in body weight gain in males and females of the mid dose and a 27-38% decrease in the high dose groups. Treated females had a slightly reduced food consumption during the first 90 days. Food efficiency for this period was slightly reduced for the male dose groups and variable for the female dosed groups (no dose response effect). At 1 year there was no treatment related effect in food consumption and at 2 years there was a slight increase in food consumption in all treated groups. There was an increase in absolute and relative liver weights at 12 and 24 months in all treated males and females; also, treated males had increased adrenal absolute and relative weights at 24 months. Spleen weights (absolute and relative) in the males and females were reduced in all treated groups. **The Systemic Toxicity LOEL is less than or equal to 250 mg/kg/day and the Systemic Toxicity NOEL less than 250 mg/kg/day based on increased liver and reduced spleen weights and gross observations in the liver of all treated animals**

Non-neoplastic observations showed an *accentuated lobular pattern* of the liver of all treated animals. There was an increase in tumor incidence in the liver in high dose males at the 12 month sacrifice (2/10, 1/9, 1/10, 5/10 for the control, low, mid and high dose groups, respectively) and in the mid and high dose males at 24 months in the form of hepatocellular adenomas (27/50, 33/50, 40/50, 41/50 for the control, low, mid and high dose groups, respectively); the females at 24 months showed a slight increase in the mid and high dose groups of hepatocellular adenomas (13/50, 14/50, 17/50, 19/50 for the control, low, mid and high dose groups, respectively).

This study is classified as Core-Minimum Data and satisfies the guideline requirements (§83-2b) for a carcinogenicity study in the mouse.

I. Toxicology Profile for Orthophenylphenol and Sodium Orthophenylphenate (40 CFR 158.340)

Technical: Orthophenylphenol and Sodium Orthophenylphenate
Use Pattern: food use

This compound is an registered active ingredient; the following data are available for Orthophenylphenol or Sodium Orthophenylphenate technical. **This table does not necessarily indicate requirements for reregistration.**

	Required	Satisfied
§81-1 Acute oral toxicity in rats	Yes	Yes
§81-2 Acute dermal toxicity in rabbits	Yes	Yes
§81-3 Acute inhalation toxicity in rats	Yes	Yes
§81-4 Primary eye irritation in rabbits	Yes	Yes
§81-5 Primary dermal irritation in rabbits	Yes	Yes
§81-6 Dermal sensitization - guinea pig	Yes	Yes
§82-1(a)90 day feeding study - rat	Yes	**NO**
§82-1(b)90 day feeding - dog	Yes	NO[1]
§82-2 21 day dermal - rabbit	Yes	Yes
§83-1(a)2-year feeding - rodent	Yes	**NO**
§83-1(b)1 year feeding - nonrodent	Yes	Yes
§83-2(a)Carcinogenicity - rat	Yes	**NO**
§83-2(b)Carcinogenicity - mouse	Yes	Yes[2]
§83-3(a)Teratology - rat	Yes	Yes
§83-3(b)Teratology - rabbit	Yes	Yes
§83-4 Multigeneration reproduction-rat	Yes	Yes
§84-2(a)Mutagenicity - Gene Mutation	Yes	Yes
§84-2(b)Muta - Struct. Chromosome Aberr.	Yes	Yes
§84-4 Muta - Other Genotoxic Effects	Yes	Yes
§85-1 General metabolism - rat	Yes	**NO**

[1] = satisfied by a chronic toxicity study
[2] = study discussed in this mem

II. Data Gaps

The following are data gaps for the technical necessary for permanent food use registration:

§82-1(a)90 day feeding study - rat
§83-1(a)2-year feeding - rodent
§83-2(a)Carcinogenicity - rat
§85-1 General metabolism - rat

III. Actions Being Taken to Obtain Additional Information or Clarification

None at this time.

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IV. Reference Dose

The Health Effects Division RfD/Peer Review Committee met on September 15, 1994 to discuss and evaluate the existing and recently submitted toxicology data in support of Ortho-phenylphenol registration and to assess the Reference Dose (RfD) for this chemical.

In the meeting of September 15, 1994, because of technical and other considerations, the RfD/Peer Review Committee's decision regarding the reassessment of the RfD was deferred pending OPP/HED's evaluation of the chronic toxicity study used in the JMPR evaluation.

The Committee recommended deletion of the existing RfD or regulatory value for this chemical from the HED files. The existing regulatory value for this chemical was generated by an Ad Hoc Committee, HED/OPP, on March 22, 1994 under special circumstances to support existing tolerances. No data or data evaluation records were available for review by the Ad Hoc Committee in the assessment of this regulatory value. The Ad Hoc Committee used the toxicology one-liner summaries to derive this value. The regulatory value was based on a developmental toxicity study in rabbits with a NOEL of 25.0 mg/kg/day (note: in a recent reevaluation by the RfD/Peer Review Committee this NOEL was raised to 100 mg/kg/day). An uncertainty factor (UF) of 100 was applied to account for inter-species extrapolation and intra-species variability. For RfD reassessment purposes, and based on technical and regulatory reasons, the chemical should now be considered under review.

It should be noted that this chemical has been reviewed by the FAO/WHO joint committee on pesticide residue (JMPR) in 1990 and an acceptable daily intake (ADI) of 0.02 mg/kg/day was established based on a chronic toxicity study in rats with a NOEL of 40 ppm (2.0 mg/kg/day). A safety factor (SF) of 100 was used to account for the inter-species extrapolation and intra-species variability.

V. Pending Regulatory Actions

None.

VI: Toxicological Issues Pertinent to this Request

A. New toxicology Data on Orthophenylphenol and Sodium Orthophenylphenate

The new study has been discussed above.

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B. Carcinogenicity

The Health Effects Division Carcinogenicity Peer Review Committee (CPRC) met on January 5, 1994 to discuss and evaluate the weight-of-the-evidence on Orthophenylphenol (OPP) and Sodium Orthophenylphenate (SOPP) with particular reference to its carcinogenic potential. The CPRC concluded that under the existing Carcinogen Risk Assessment guidelines, the evidence for OPP & SOPP is sufficient for classification as **Group B2 - probable human carcinogen**, based on evidence of multiple tumor types in multiple sites.

However, in consideration of what is known about the metabolism of these compounds and the anticipated human exposure, the CPRC felt that it was inappropriate to apply a low-dose extrapolation methodology (Q*) to the animal data. Therefore, the CPRC recommended the use of the **Margin of Exposure (M.O.E.)** methodology to be applied for the estimation of human risk, for the time being. Review of recently submitted 6(a)(2) data from the mouse carcinogenicity study may lead to a reconsideration of this interim decision.

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Primary Review by: Stephen C. Dapson, Ph.D. Stephen C. Dapson 11/15/95
Senior Pharmacologist, Review Section I, TBII (7509C)

Secondary Review by: Yiannakis M. Ioannou, Ph.D., D.A.B.T. Y.M. Ioannou 12/6/95
Section Head, Review Section I, TBII (7509C)

DATA EVALUATION RECORD

Study Type: Chronic Oral (Feeding) Toxicity/Carcinogenicity
Species: Mouse Guideline: §83-5

EPA Numbers: EPA MRID# 43545501
EPA Pesticide Chemical Code 064103
Toxicology Chemical No. 623AA
EPA Reregistration Case # 2575
EPA DP Barcode D212562
EPA Submission Barcode S482630

Test Material: ORTHO-PHENYLPHENOL

Title of Report: ORTHO-PHENYLPHENOL: TWO-YEAR DIETARY CHRONIC TOXICITY/ONCOGENICITY STUDY IN B6C3F1 MICE

Sponsor: Specialty Chemicals/Performance Products, The Dow Chemical Company, Midland, Michigan 48674 and Miles Inc., Stillwell, Kansas

Testing Facility: The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, MI 48674 and Health and Environmental Sciences-Texas, The Dow Chemical Company, Lake Jackson Research Center, Freeport, Texas 77541

Study Number: Laboratory Project Study ID K-001024-047

Author(s): J.F. Quast, R.J. McGuirk

Report Issued: February 1, 1995

Executive Summary: In a carcinogenicity study (MRID# 43545501) B6C3F1 albino mice (50/sex/dose group) from Charles River Laboratory, Portage, MI received ORTHO-PHENYLPHENOL (99.88% a.i.; Lot# 8800005-24, mixture of Dow Chemical Company and Miles, Inc. products) in the diet for 24 months at dose levels of 0, 250, 500 and 1000 mg/kg/day. A satellite group of ten animals/sex/dose group were sacrificed at 12 months.

Systemic toxicity was noted in treated females at 3 months as decreased body weight gain (10-12%), statistically significant but not dose related. At 12 and 24 months there was a 14-25% decrease in body weight gain in males and females of the mid dose and a 27-38% decrease in the high dose groups. Treated females

had a slightly reduced food consumption during the first 90 days. Food efficiency for this period was slightly reduced for the male dose groups and variable for the female dosed groups (no dose response effect). At 1 year there was no treatment related effect in food consumption and at 2 years there was a slight increase in food consumption in all treated groups. There was an increase in absolute and relative liver weights at 12 and 24 months in all treated males and females; also, treated males had increased adrenal absolute and relative weights at 24 months. Spleen weights (absolute and relative) in the males and females were reduced in all treated groups. **The Systemic Toxicity LOEL is less than or equal to 250 mg/kg/day and the Systemic Toxicity NOEL less than 250 mg/kg/day based on increased liver and reduced spleen weights and gross observations in the liver of all treated animals**

Non-neoplastic observations showed an *accentuated lobular pattern* of the liver of all treated animals. There was an increase in tumor incidence in the liver in high dose males at the 12 month sacrifice (2/10, 1/9, 1/10, 5/10 for the control, low, mid and high dose groups, respectively) and in the mid and high dose males at 24 months in the form of hepatocellular adenomas (27/50, 33/50, 40/50, 41/50 for the control, low, mid and high dose groups, respectively); the females at 24 months showed a slight increase in the mid and high dose groups of hepatocellular adenomas (13/50, 14/50, 17/50, 19/50 for the control, low, mid and high dose groups, respectively).

This study is classified as Core-Minimum Data and satisfies the guideline requirements (§83-2b) for a carcinogenicity study in the mouse.

A. Materials and Methods: A copy of the Materials and Methods section from the investigators report is attached.

1. Test compound: ORTHO-PHENYLPHENOL
Description - white to pink solid
Lot # - 8800005-24 (mixture of Dow Chemical Company and Miles, Inc.)
Purity - 99.88%

2. Vehicle(s): not provided

3. Test animals: Species: albino mouse
Strain: B6C3F1
Age: 5 weeks
Weight: 24.4-24.6 g for males; 20.2-20.6 g for females
Source: Charles River Laboratory, Portage MI

4. Animal husbandry

Animals were kept under standard animal care conditions (see attached material and methods section) and were quarantined for a period of 1 week prior to use. They received Purina Mills Certified Rodent Diet #5002 (Richmond, IN) and tap water, *ad libitum*.

5. Animal assignment

Animals were randomly assigned to the following test groups using a computerized, weight-stratification and random-number based procedure:

Test Group	Dose in diet (mg/kg/day)	Main Study 24 months male	female	Interim Sac. 12 months male	female
1 Control	0	50	50	10	10
2 Low (LDT)	250	50	50	10	10
3 Mid (MDT)	500	50	50	10	10
4 High (HDT)	1000	50	50	10	10

6. Diet preparation

Diet was prepared weekly or every other week and stored at room temperature. Samples of treated food were analyzed for stability, concentration, homogeneity and dose level verification.

7. Observations

Animals were inspected once daily for mortality, moribundity and for signs of toxicity. Detailed observations for signs of toxicity were conducted weekly. Body weights and feed crock weights were recorded once weekly for the first 13 weeks and monthly thereafter. Food efficiency was calculated for the first 13 weeks.

8. Ophthalmological examinations

Ophthalmological examinations were performed.

9. Hematology and clinical chemistry

Blood was collected by orbital sinus puncture at 12 and 24 months for hematology and clinical analysis from all survivors in the satellite group and from 10 animals/sex/dose level at study termination. The following parameters were examined:

a. Hematology

Hematocrit (HCT)*, hemoglobin (HGB)*, erythrocyte count (RBC)*, leukocyte count (WBC)*, platelet count*, and leukocyte differential count*.* **Required for chronic studies**

b. Clinical chemistry

Alanine aminotransferase (also SGPT/ALT)*, alkaline phosphatase (ALK), aspartate aminotransferase (also SGOT/AST)*, blood urea nitrogen*, total cholesterol*, total protein (TP)*, albumin*, creatinine*, total bilirubin, glucose*, globulin, sodium*, potassium*, chloride*, calcium*, and inorganic phosphorous*.* **Required for chronic studies**

The following parameter required for chronic studies was not measured:creatinine phosphokinase*; however, the lack of this determination will not affect the outcome of the review of this study.

c. Urinalysis

Urine samples were collected from nonfasted surviving mice at the 12 month sacrifice and 10 mice/sex/dose group one week before the 24 month sacrifice. The following parameters were measured: appearance*, volume*, specific gravity*, pH, bilirubin*, glucose*, protein*, ketones*, blood*, urobilinogen, and sediment (microscopic)*.* **Required for chronic studies**

10. Sacrifice and Pathology

All animals that died and that were sacrificed on schedule were subject to gross pathological examination consisting of both external and internal examination. The following tissues were collected for histological examination. The **bolded** organs, in addition, were weighed.

Adrenal glands*, aorta*, bone and joint, bone marrow, **brain***+, cecum*, cervix, coagulating glands, colon*, duodenum*, epididymides, esophagus*, eye and optic nerve*, gall bladder*, gross lesions and masses*, **heart***, ileum*, jejunum*, **kidneys***+, lacrimal/harderian glands, larynx, **liver***+, lungs*, mammary glands, mediastinal lymph node*, mediastinal tissue, mesenteric lymph node*, mesenteric tissue, nasal tissue, oral tissue, ovaries*+, oviducts, pancreas*, parathyroid glands*, peripheral nerve*, pituitary gland*, prostate, rectum*, salivary glands*, seminal vesicles, skeletal muscle*#, nasal turbinates, skin and subcutis*, **spleen**, spinal cord*# (cervical, thorax, lumbar), stomach*, **testes***+, thymus*, thyroid gland*, tongue, trachea* urinary bladder*, uterus* and vagina.

*** Required for subchronic and chronic studies.**

+ Organ weight required in chronic studies.

11. Statistics

The following procedures were utilized in analyzing the numerical data (from the investigators report, pages 32-34 of the report):

> Hematology (excluding differential counts) data, body weights, body weight gains from baseline, clinical chemistry and electrolyte determinations, urine specific gravity, and absolute (grams) and relative (g to 100 g terminal body weight) organ weights were evaluated by Bartlett's test (Winer, 1971) for equality of variances. Based on the outcome of Bartlett's test, exploratory data analysis was performed by a parametric or non-parametric analysis of variance (ANOVA; Steel and Torrie, 1960), followed, when appropriate, by Dunnett's t test (Steel and Torrie) or Wilcoxon rank-sum test (Steel and Torrie) with Bonferroni's correction (Miller, 1966) for multiple comparisons. Statistical outliers were identified by a sequential test described by Grubbs (1969), but routinely excluded only from feed consumption data. Statistical outliers were excluded from other means only for documented, scientifically sound reasons, unrelated to treatment Feed consumption and feed efficiency data, which was used in the computation of desired test material concentrations and shown in the final report, was not analyzed for

differences of statistical significance. Descriptive statistics (means and standard deviations) only were reported for WBC differential counts.

The nominal alpha levels used and the test references are as follows:

Name of the test and (Reference)	Alpha=
Bartlett's test (Winer, 1971)	0.01
Parametric ANOVA (Steel & Torrie, 1960)	0.10
Nonparametric ANOVA (Hollander & Wolfe, 1973)	0.10
Dunnett's test (Winer, 1971)	0.05, two-sided
Wilcoxon Rank-Sum (Hollander & Wolfe, 1973) Bonferroni correction (Miller, 1966)	0.05, two-sided
Outlier test (Grubbs, 1969)	0.02, two-sided

As an oncogenicity study in rodents nears its end, statistical analyses are confounded by a spectrum of geriatric changes, the presence of spontaneous tumors and secondary effects of tumors, and changes prior to death. As a result, statistical tests in the latter part of a study are of questionable value, and extra caution must be taken in the interpretation of any statistical result. Because of the need to satisfy regulatory requirements, and despite the aforementioned limitations, the data generated in the latter part of this study were statistically analyzed.

Gross pathologic observations were tabulated and considered in the interpretation of final histopathologic data but were not analyzed statistically. However, the cumulative incidence of appropriate histopathologic observations on all animals scheduled for the chronic toxicity/oncogenicity portion of the study were statistically analyzed. For tissues where all animals in all dose groups were scheduled to be examined, the incidences of specific observations were first tested for deviation from linearity using ordinal spacings of the doses. If linearity was not rejected, the data were then tested for linear trend using the Cochran-Armitage Trend test. If the trend was statistically significant, or if significant deviation from linearity was found, incidences for each dose group were compared to those of the control group using a pairwise Chi-square test with Yates' continuity correction.

For tissues evaluated in all control and high dose mice, but only from selected mice in the lower dose groups, statistical analysis was limited to the pairwise comparisons of control and high dose using the pairwise Chi-square test with Yates's continuity correction.

Differences in mortality patterns were tested by the Gehan-Wilcoxon procedure (Breslow, 1970: $\alpha = 0.05$) on data from all animals scheduled for the 24-month sacrifice. Since no differences were detected in mortality patterns in any group, no further statistical analyses for mortality adjustment of tumor histopathology was necessary.

The nominal alpha levels used and the test references are as follows:

Name of Test and (Reference)	Alpha=
Chi square for lack of linearity (Armitage, 1971)	0.01
Trend test (Armitage, 1971)	0.02, two-sided
Pairwise Chi square Comparison test with Yates' continuity correction (Fleiss, 1981)	0.05, two-sided
Gehan-Wilcoxon (Breslow, 1970)	0.05

When multiple grades of a histologic observation were given, each grade and the total number of animals with any grade was analyzed. This served to evaluate any exposure-related exacerbation of commonly occurring lesions. Observations made on tissues or organs that were examined only because of a grossly observed lesion were not analyzed statistically, and no analyses was performed on "secondary tumors," i.e., metastatic sites.

Because numerous measurements were compared statistically on the same group of animals, the frequency of false-positive (Type I) errors was unknown, but was much greater than the nominal alpha levels shown. The final toxicologic interpretation of the data considered other factors, such as dose-response relationships, biological plausibility, and consistency.

12. Compliance

A signed and dated STATEMENT OF NO CONFIDENTIALITY CLAIMS, COMPLIANCE WITH GOOD LABORATORY PRACTICE STANDARDS statement, FLAGGING STATEMENT FOR POTENTIAL ADVERSE EFFECTS (the study meets or exceeds the criteria numbered 1 in 40 CFR 158.34), and QUALITY ASSURANCE STATEMENT were provided.

B. Results

1. Analysis of dietary mixtures

The following description provides the results of the dietary analysis (from page 35 of the investigators report) and attached as an appendix are the tables of stability, homogeneity and concentration analysis (Tables 4, 5, and 6 of the investigators report):

Test Material Analyses Prior to initiation of the study, the purity of the test material was determined to be 99.88% (Becker, 1990). In addition, the stability of OPP was confirmed repeatedly by analyzing for purity four times during the study and once after study completion (Table 3). In every instance the values for purity/stability exceeded 99.74%.

Stability, Homogeneity and Concentration Checks The stability of OPP in basal rodent chow was determined to be at least 28 days when stored at room temperature (Table 4).

Analytical results confirmed that mixing methods used for diet preparation had homogeneously dispersed OPP within the feed (Table 5).

Repeated analyses to verify the concentrations of OPP in the diet were conducted prestudy and approximately every three months thereafter (Table 6). Overall for the study, diets were 96-100% of the targeted concentration.

2. Observations

a. Mortality

i. Satellite group

One low dose male mouse died on study day 14, due to unknown causes. All other animals survived to the 12 month sacrifice.

ii. Carcinogenicity group

At study termination cumulative mortality in males was 8, 10, 13, and 11 out of 50 animals per dose group for the control, low, mid and high dose groups, respectively; for the females cumulative mortality was 14, 20, 22, and 14 out of 50 animals per dose group for the control, low, mid and high dose groups, respectively. No treatment related effect on mortality or cause of death was noted.

4. Food consumption, food efficiency and compound intake

The investigators provided group mean, graphed group mean and individual animal data. The following table presents food consumption data (in grams per day) and food efficiency:

Day	Group:	Control	Low	Mid	High
92	M	4.5	4.9	4.9	5.1
	F	7.5	7.1	7.2	6.6
365	M	4.6	4.2	4.2	4.4
	F	5.3	4.8	5.8	5.6
729	M	4.1	4.8	4.5	5.9
	F	3.8	5.0	6.0	4.9
Food efficiency at 13 weeks					
	M	189.4	92.3	95.1	122
	F	108.6	165.3	394.8	111.3

Data extracted from Study ID: K-001024-047, Tables 21-24, pages 106-115 of the report.

Food consumption at 92 days was slightly increased in the high dose males and slightly decreased in the high dose females. Food efficiency for this period for male and female mice was variable and no meaningful conclusions could be drawn from these data. At 1 year there was no treatment related effect in food consumption and at 2 years there was a slight increase in food consumption in all treated groups (again, no dose response relationship).

5. Hematology and clinical chemistry

The investigators provided group summary and individual animal data.

a. Hematology

i. Satellite group

There was a statistically significant increase in platelets in the mid dose group; however, the biological relevance of this finding is unclear. This was not seen at the 24 month sacrifice and this observation is not considered to be related to treatment. No other parameter was affected.

ii. Carcinogenicity group

There was a statistically significant increase in platelets in the high dose females, this observation is not considered treatment related since it was not seen at 12 months and not observed in males. No other parameter was affected.

b. Clinical chemistry

i. Satellite group

Alkaline phosphatase was statistically significantly increased in all dosed males (dose-related) and there was a dose related increase in all dosed females with the high dose group being statistically significant. Mid dose males had a statistically significant decrease in alanine aminotransferase, low dose males had a statistically significant increase in glucose and the high dose females had statistically significantly decreased glucose levels, there was a dose related increase in calcium levels in all dose females (with the mid and high dose groups statistically significantly different) along with a statistically significant increase in inorganic phosphate levels (not dose related) in all treated females; however, with no specific related pathology, the biological relevance of these observations is unclear. Also, most of these findings were not observed at 24 months.

ii. Carcinogenicity group

The urea nitrogen levels in the mid dose males was statistically significantly decreased, the low and mid dose male glucose levels were statistically significantly increased; again as discussed for the satellite group, there was no specific related pathology, therefore the biological relevance of these observations is unclear.

c. Urinalysis

No effects of treatment were noted at 12 months. At 24 months there was a dose related decrease in the dosed females specific gravity (statistically significant decrease in the mid and high dose females). The investigators feel that this is due to...*normal variation for mice of this strain and age*; however, no historical control data were supplied. Also, the urinary tract is the target organ for OPP and SOPP in other species; however, the biological relevance of this observation is unclear.

6. Pathology

a. Gross pathological observations

No treatment related effects were noted in the satellite group. In the carcinogenicity group there was an increased incidence of liver mass/nodule in the male mid and high dose groups as compared to the control. The following table presents selected observations:

Incidence of Mass/Nodule in Male and Female Mice at 12 and 24 months

Observation Group:	Control	Low	Mid	High
12 months				
(#males/females examined)	10/10	10/10	10/10	9/10
Kidneys	0/0	1/0	0/0	0/0
Liver	1/0	1/1	1/0	5/1
24 months	50/50	50/50	50/50	50/50
External and skin	0/1	0/2	1/2	1/3
Ileum	0/0	0/0	0/0	1/0
Jejunum	1/0	1/1	2/0	1/0
Kidney	1/0	0/0	0/1	0/0
Liver	29/12	30/20	38/19	38/21
Lungs	14/4	13/4	9/5	11/7
Lymph nodes	0/0	0/0	0/1	0/0
Mammary gland	0/1	0/1	0/0	0/1
Ovaries	1	1	2	1
Pancreas	0/0	0/0	0/0	0/1
Pituitary	0/1	0/0	0/1	0/1
Preputial or clitoral glands	0/0	0/0	1/1	0/0
Salivary gland	0/0	0/0	0/1	0/0
Spleen	0/1	2/4	2/1	1/0
Thyroid gland	1/0	0/0	0/0	0/0
Uterus	0	2	3	3
Vagina	0	0	1	2

Data extracted from Study ID: K-001024-047, Tables 41 and 44, pages 146, 158-164 of the report.

b. Organ weight

The investigators provided group summary and individual animal data. The following table presents selected organs:

Organ	Group:	Control	Low	Mid	High
			12 months		
Kidney(s)					
M[1]	Ab[2]	0.809	0.780	0.699*	0.667*
	Rel[3]	1.749	1.721	1.727	1.651
F[4]	Ab	0.539	0.562	0.561	0.548
	Rel	1.225	1.387*	1.395*	1.580*
Liver					
M	Ab	2.341	2.730	2.513	2.924*
	Rel	5.037	5.970*	6.200*	7.208*
F	Ab	1.914	2.089*	2.233*	2.426*
	Rel	4.335	5.151*	5.549*	6.984*

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Organ	Group:	Control	Low	Mid	High
			24 months		
Adrenal(s)					
M	Ab	0.0066	0.0077*	0.0071	0.0088*
	Rel	0.0151	0.0175*	0.0179*	0.0227*
F	Ab	0.0100	0.0085*	0.0090	0.0086*
	Rel	0.0246	0.0220	0.0252	0.0257
Brain					
M	Ab	0.498	0.500	0.503	0.509*
	Rel	1.147	1.136	1.259*	1.325*
F	Ab	0.507	0.510	0.512	0.512
	Rel	1.251	1.337	1.443*	1.537*
Kidney(s)					
M	Ab	0.782	0.796	0.731*	0.669*
	Rel	1.791	1.806	1.817	1.736
F	Ab	0.571	0.583	0.592	0.566
	Rel	1.417	1.518	1.665*	1.697*
Liver					
M	Ab	2.722	2.905	3.118	3.031
	Rel	6.469	6.677	7.948	7.862
F	Ab	1.941	2.161	2.650*	2.384*
	Rel	4.837	5.626*	7.526*	7.076*
Spleen					
M	Ab	0.153	0.210	0.109*	0.091*
	Rel	0.379	0.502	0.293	0.236
F	Ab	0.479	0.374	0.277	0.294
	Rel	1.257	0.997	0.763	0.891

* = $p < 0.05$; [1] = males; [2] = absolute organ weight in g; [3] = relative organ weight in g/100; [4] = females; Data extracted from Study ID: K-001024-047, Tables 37 to 40, pages 140-145 of the report.

Treatment related observations were: increased absolute and relative liver weights at 12 and 24 months in all treated males and females and increased absolute and relative adrenal weights at 24 months in treated males. Spleen weights (absolute and relative) in the males and females were reduced in all treated groups. Other differences noted, not necessarily related to treatment, were: at 12 months, increased relative brain weights in the mid and high dose males and high dose females (no differences in absolute weights), decreased absolute heart weights in the mid and high dose males and decreased absolute heart weights in the high dose females (no differences in relative weights), and decreased relative testes weights in the mid and high dose males (no differences in absolute weights). At 24 months there were increased relative testes weights in the high dose males and increased relative heart weights in the mid and high dose males (no differences in absolute weights).

c. Microscopic pathology

i. Non-neoplastic observations

The investigators provided group mean and individual animal data. The following table presents selected non-neoplastic observations:

Observation Group:	Control	Low	Mid	High
12 months				
(# males/females examined)	**10/10**	**9/10**	**10/10**	**10/10**
Liver				
Accentuated lobular pattern	0/0	4/7	9/10	10/9
Ovaries				
Cysts	1	-	1	3
24 months	**50/50**	**50/50**	**50/50**	**48/50**
Liver				
Accentuated lobular pattern	12/7	34*/14	35*/26*	37*/37*

*** = p < 0.05 as compared to the control; Data extracted from Study ID: K-001-24-047, Tables 42 and 45, pages 147-156 and 165-197 of the study report.**

Non-neoplastic observations showed an *accentuated lobular pattern* of the liver of all treated animals.

ii. Neoplastic observations

The investigators provided group mean and individual animal data. The following table presents all reported neoplastic observations:

Observation Group:	Control	Low	Mid	High
12 months				
(# males/females examined)	**10/10**	**9/10**	**10/10**	**10/10**
Liver				
Hepatocellular adenoma	2/0	1/2	1/0	5/1
Lungs				
Bronchoalveolar adenoma	0/0	1/0	1/0	1/1
Skin				
Undifferentiated sarcoma	0/0	-/-	-/-	1/0

Observation Group:	Control	Low	Mid	High
24 months (# males/females examined)	50/50	50/50	50/50	48/50
Epididymides (#examined)	50	10	13	50
Leydig cell tumor	1	0	0	2
Liver				
Bile duct adenocarcinoma	0/0	1/0	0/0	0/0
Hepatocellular adenoma	27/13	33/14	40*/17	41*/19
Hepatocellular carcinoma	11/2	5/8	14/6	12/5
Hemangioma	1/1	4/1	0/1	2/0
Hemangiosarcoma	2/0	1/1	0/0	2/0
Liposarcoma	0/0	0/0	0/0	1/0
Histiocytic sarcoma	0/0	0/0	1/0	0/0
Lymphosarcoma	0/1	0/1	0/0	0/0
Hepatoblastoma	0/0	2/0	6/0	3/0
Lungs				
Bronchoalveolar adenocarc.	6/2	2/2	0/0	1/1
Bronchoalveolar adenoma	14/5	13/6	12/4	11/6
Pituitary (#examined)	48/43	10/19	10/22	40/43
Adenoma, pars distalis	0/6	0/0	0/1	1/4
Adenoma, pars intermedia	0/0	0/0	0/0	0/1

* = p < 0.05 as compared to the control; Data extracted from Study ID: K-001-24-047, Tables 42 and 45, pages 147-156 and 165-197 of the study report.

There was an increase in tumor incidence in the liver in high dose males at the 12 month sacrifice and in the mid and high dose males at 24 months in the form of hepatocellular adenomas; the females at 24 months had a slight increase of hepatocellular adenomas in the mid and high dose groups. Attached as an appendix are Tables 44 and 46 from the investigators report which present a summary of the tumor incidence at 12 and 24 months, these tables provide the above presented tumor data and appropriate combinations of tumors at specific sites (liver combined tumors are increased in the mid and high dose males).

C. Discussion/Conclusions

Systemic toxicity was noted in treated females at 3 months as decreased body weight gain (10-12%), statistically significant but not dose related. At 12 and 24 months there was a 14-25% decrease in body weight gain in males and females of the mid dose and a 27-38% decrease in the high dose groups. Treated females had a slightly reduced food consumption during the first 90 days. Food efficiency for this period was slightly reduced for the male dose groups and variable for the female dosed groups (no dose response effect). At 1 year there was no treatment related effect in food consumption and at 2 years there was a slight increase in food consumption in all treated groups. There was an increase in absolute and relative liver weights at 12 and 24 months in all treated males and females; also, treated males had increased adrenal absolute and relative weights at 24 months. Spleen weights (absolute and relative) in the males and females were reduced in all treated groups.

Non-neoplastic observations showed an *accentuated lobular pattern* of the liver of all treated animals. There was an increase in tumor incidence in the liver in high dose males at the 12 month sacrifice (2/10, 1/9, 1/10, 5/10 for the control, low, mid and high dose groups, respectively) and in the mid and high dose males at 24 months in the form of hepatocellular adenomas (27/50, 33/50, 40/50, 41/50 for the control, low, mid and high dose groups, respectively); the females at 24 months showed a slight increase in the mid and high dose groups of hepatocellular adenomas (13/50, 14/50, 17/50, 19/50 for the control, low, mid and high dose groups, respectively).

Systemic Toxicity NOEL < 250 mg/kg/day
Systemic Toxicity LOEL <= 250 mg/kg/day

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TABLE 4
ORTHO-PHENYLPHENOL: TWO-YEAR DIETARY CHRONIC TOXICITY/ONCOGENICITY STUDY IN B6C3F1 MICE

STABILITY OF TEST MATERIAL IN RODENT CHOW

DAY	OBSERVED (UG/G)[a]	%OF DAY ZERO
0	$(1.48 \pm 0.01) \times 10^3$	NOT APPLICABLE
7	$(1.37 \pm 0.02) \times 10^3$	93
14	$(1.51 \pm 0.03) \times 10^3$	102
28	$(1.44 \pm 0.04) \times 10^3$	97

[a]SAMPLES TAKEN FROM THE 250 MG/KG/DAY FEMALE DIET MIXED ON 11-13-91 (TARGET CONCENTRATION = 1.521 UG/G). THE RESULTS OF THE STABILITY ANALYSIS INDICATED THE TEST MATERIAL WAS STABLE IN RODENT CHOW FOR AT LEAST 28 DAYS (CAMPBELL, 1992).

TABLE 5
ORTHO-PHENYLPHENOL: TWO-YEAR DIETARY CHRONIC TOXICITY/ONCOGENICITY STUDY IN B6C3F1 MICE

HOMOGENEITY OF TEST DIETS

SAMPLE[a]	LOCATION	OBSERVED CONCENTRATION (MEAN±STD DEV)(UG/G)	PERCENT OF TARGET (%)
SIDE	TOP	$(1.46 \pm 0.01) \times 10^3$	96
SIDE	BOTTOM	$(1.49 \pm 0.02) \times 10^3$	98
CENTER	TOP	$(1.48 \pm 0.01) \times 10^3$	97
CENTER	BOTTOM	$(1.47 \pm 0.01) \times 10^3$	96
	MEAN S.D.=	**$(1.48 \pm 0.01) \times 10^3$**	**97**

[a]SAMPLES TAKEN FROM THE 250 MG/KG/DAY FEMALE DIET MIXED ON 11-13-91 (TARGET CONCENTRATION = 1.521 UG/G). THE RESULTS OF THE HOMOGENEITY ANALYSIS INDICATED THE TEST MATERIAL WAS HOMOGENEOUSLY DISTRIBUTED IN THE RODENT CHOW (CAMPBELL 1991).

TABLE 6
ORTHO-PHENYLPHENOL: TWO-YEAR DIETARY CHRONIC TOXICITY/ONCOGENICITY STUDY IN B6C3F1 MICE

CONCENTRATION CHECKS OF TEST MATERIAL IN DIETS

DIET	% OF TARGET[a]											
	11-13-91	2-5-92	5-6-92	8-12-92	11-11-92	11-18-92	2-10-93	5-5-93	8-11-93	11-3-93	MEAN	S. D.
PREMIX	97	101	97	100	99	99	101	100	99	103	99.6	1.84
1000 MALE	98	98	95	98	98	95	98	96	96	102	97.4	2.07
500 MALE	103	97	95	100	89	100	97	94	93	102	97.0	4.37
250 MALE	98	99	92	100	109	101	95	95	93	103	98.5	5.13
1000 FEMALE	98	98	95	98	98	98	97	94	96	102	97.4	2.17
500 FEMALE	97	99	94	98	98	98	96	95	93	97	96.5	1.96
250 FEMALE	97	102	97	99	100	97	95	92	92	103	97 4	3 75

CONTROL (not detected at time points measured above)

[a]THE DATES INDICATE THE DAY THE DIETS WERE MIXED. THE RESULTS OF THE CONCENTRATION CHECKS INDICATED THE TEST DIETS WERE WITHIN APPROXIMATELY 10% OF THE TARGETED CONCENTRATIONS.
LIMITS OF DETECTION = 39.05 - 1000 UG/G.

TABLE 43
ORTHO-PHENYLPHENOL: TWO-YEAR DIETARY CHRONIC TOXICITY/ONCOGENICITY STUDY IN B6C3F1 MICE

TUMOR INCIDENCE - 12 MONTHS

SEX	MALES				FEMALES			
DOSE IN MG/KG/DAY	0	250	500	1000	0	250	500	1000
NUMBER OF MICE EXAMINED	10	9	10	10	10	10	10	10
LIVER (NO. OF TISSUES EXAMINED)	10	9	10	10	10	10	10	10
ADENOMA, HEPATOCELLULAR, BENIGN, PRIMARY:	1	1	1	5	0	2	0	1
ADENOMA, HEPATOCELLULAR, BENIGN, PRIMARY: (TWO)	1	0	0	0	0	0	0	0
ADENOMA, HEPATOCELLULAR, BENIGN, PRIMARY: **	2	1	1	5	0	2	0	1
LUNGS (NO. OF TISSUES EXAMINED)	10	9	10	10	10	10	10	10
ADENOMA, BRONCHIOLOALVEOLAR, BENIGN, PRIMARY:	0	1	1	1	0	0	0	1
SKIN AND SUBCUTIS (NO. OF TISSUES EXAMINED)	10	0	0	10	10	0	0	0
UNDIFFERENTIATED SARCOMA, MALIGNANT, PRIMARY, NO METASTASIS:	0	-	-	1	0	-	-	0

DATA ARE THE NUMBER OF ANIMALS WITH THE SPECIFIED OBSERVATION
** THIS LINE REPRESENTS THE COMBINATION OF TWO OR MORE PRECEDING LINES WITH SIMILAR OBSERVATIONS AND LOCATORS.

TABLE 46
ORTHO-PHENYLPHENOL: TWO-YEAR DIETARY CHRONIC TOXICITY/ONCOGENICITY STUDY IN B6C3F1 MICE
TUMOR INCIDENCE - 24 MONTHS

SEX	MALES				FEMALES			
DOSE IN MG/KG/DAY	0	250	500	1000	0	250	500	1000
NUMBER OF MICE EXAMINED	50	50	50	50	48	50	50	50
ADRENALS (NO. OF TISSUES EXAMINED)	50	10	13	50	48	20	23	50
ADENOMA, CORTEX, BENIGN, PRIMARY:	0	0	0	0	1	0	1	0
CARCINOMA, HEPATOCELLULAR, MALIGNANT, SECONDARY:	0	0	1	0	0	0	0	0
PHEOCHROMOCYTOMA, MEDULLA, BENIGN, PRIMARY:	0	0	0	0	1	0	0	0
PHEOCHROMOCYTOMA, MEDULLA, MALIGNANT, PRIMARY, METASTASIS:	0	0	0	1	0	0	0	0
PHEOCHROMOCYTOMA, MEDULLA, BENIGN OR MALIGNANT, PRIMARY, METASTASIS:	0	0	0	1 **	1	0	0	0
SPINDLE CELL TUMOR CORTEX, BENIGN, PRIMARY:	1	0	0	0	1	0	0	0
SPINDLE CELL TUMOR CORTEX, MALIGNANT, PRIMARY, NO METASTASIS:	0	0	0	0	0	0	1	0
SPINDLE CELL TUMOR, CORTEX, BENIGN OR MALIGNANT, PRIMARY, NO METASTASIS:	1	0	0	0 **	1	0	1	0
BONE (NO. OF TISSUES EXAMINED)	50	10	13	50	48	20	22	50
HEMANGIOMA, STERNUM, BENIGN, PRIMARY:	0	0	0	0	0	0	1	0
HEMANGIOSARCOMA, VERTEBRAE, MALIGNANT, PRIMARY, NO METASTASIS:	1	0	0	0	0	0	0	0
OSTEOGENIC SARCOMA, RIB, MALIGNANT, PRIMARY, NO METASTASIS:	1	0	0	0	0	0	0	0
OSTEOGENIC SARCOMA, RIB, MALIGNANT, PRIMARY, METASTASIS:	0	0	0	0	0	1	0	0
OSTEOGENIC SARCOMA, RIB, MALIGNANT, PRIMARY, METASTASIS OR NO METASTASIS:	1	0	0	0 **	0	1	0	0
OSTEOGENIC SARCOMA, STERNUM, MALIGNANT, PRIMARY, NO METASTASIS:	0	0	0	0	1	0	0	0
BRAIN (NO. OF TISSUES EXAMINED)	50	10	13	50	48	20	22	50
MENINGIOSARCOMA, MALIGNANT, PRIMARY, NO METASTASIS:	0	0	0	0	1	0	1	0
CECUM (NO. OF TISSUES EXAMINED)	50	10	13	50	48	20	22	50
LEIOMYOMA, BENIGN, PRIMARY:	0	0	0	0	0	0	0	1
CERVIX (NO. OF TISSUES EXAMINED)					48	20	22	50
FIBROSARCOMA, MALIGNANT, PRIMARY, NO METASTASIS:					2	0	0	0
STROMAL CELL SARCOMA, MALIGNANT, PRIMARY, NO METASTASIS:					1	0	0	0
DUODENUM (NO. OF TISSUES EXAMINED)	50	10	13	50	48	20	22	50
ADENOMA, BENIGN, PRIMARY:	0	0	0	0	1	0	0	0
EPIDIDYMIDES (NO. OF TISSUES EXAMINED)	50	10	13	50				
LEYDIG CELL TUMOR, TAIL, BENIGN, PRIMARY:	1	0	0	1				
LEYDIG CELL TUMOR, TAIL, BENIGN, PRIMARY:	0	0	0	1				
LEYDIG CELL TUMOR, TAIL, BENIGN, PRIMARY:	1	0	0	2 **				

continued

TABLE 46 continued
ORTHO-PHENYLPHENOL: TWO-YEAR DIETARY CHRONIC TOXICITY/ONCOGENICITY STUDY IN B6C3F1 MICE
TUMOR INCIDENCE - 24 MONTHS

SEX	MALES					FEMALES			
DOSE IN MG/KG/DAY	0	250	500	1000		0	250	500	1000
NUMBER OF MICE EXAMINED	50	50	50	50		48	50	50	50
EYES (NO. OF TISSUES EXAMINED)	50	10	13	50		48	20	22	50
ADENOCARCINOMA, BILE DUCT(S), MALIGNANT, SECONDARY:	0	1	0	0		0	0	0	0
HEART (NO. OF TISSUES EXAMINED)	50	10	13	50		48	20	22	50
HEMANGIOMA, BENIGN, PRIMARY:	0	0	0	0		0	0	1	0
ILEUM (NO. OF TISSUES EXAMINED)	50	11	13	50		48	20	22	50
LYMPHOSARCOMA, PEYER'S PATCH, MALIGNANT, PRIMARY, NO METASTASIS:	0	1	0	0		0	0	0	0
LACRIMAL/HARDERIAN GLAND(S) (NO. OF TISSUES EXAMINED)	50	16	15	50		48	26	23	50
ADENOCARCINOMA, MALIGNANT, PRIMARY, NO METASTASIS:	1	1	0	1		0	0	0	0
ADENOMA, BENIGN, PRIMARY:	7	5	3	4		3	5	1	4
ADENOMA, BENIGN, PRIMARY: (TWO)	1	1	0	0		0	0	0	0
ADENOMA, BENIGN, PRIMARY:	8	6	3	4	**	3	5	1	4
CYSTADENOMA, BENIGN, PRIMARY:	0	0	0	0		0	1	0	0
ADENOMA/CYSTADENOMA AND/OR ADENOMACARCINOMA	9	7	3	5		3	6	1	4
LIVER (NO. OF TISSUES EXAMINED)	50	50	50	50		48	50	50	50
ADENOCARCINOMA, BILE DUCT(S), MALIGNANT, PRIMARY, METASTASIS:	0	1	0	0		0	0	0	0
ADENOMA, HEPATOCELLULAR, BENIGN, PRIMARY:	17	11	13	15		9	8	8	10
ADENOMA, HEPATOCELLULAR, BENIGN PRIMARY: (TWO)	4	1	12	8		3	5	4	7
ADENOMA, HEPATOCELLULAR, BENIGN PRIMARY: (THREE)	1	3	6	6		0	0	1	0
ADENOMA, HEPATOCELLULAR, BENIGN, PRIMARY: (FOUR)	1	4	3	2		0	0	1	2
ADENOMA, HEPATOCELLULAR, BENIGN, PRIMARY: (FIVE)	1	4	3	2		0	0	1	0
ADENOMA, HEPATOCELLULAR, BENIGN, PRIMARY:	27	33	40*	41*T	**	13	14	17	19
CARCINOMA, HEPATOCELLULAR, MALIGNANT, PRIMARY, NO METASTASIS:	9	3	3	7		1	6	4	3
CARCINOMA, HEPATOCELLULAR, MALIGNANT, PRIMARY, METASTASIS:	2	2	6	5		1	2	2	2
CARCINOMA, HEPATOCELLULAR, MALIGNANT, PRIMARY, METASTASIS: (TWO)	0	0	4	0		0	0	0	0
CARCINOMA, HEPATOCELLULAR, MALIGNANT, PRIMARY, METASTASIS: (THREE)	0	0	1	0		0	0	0	0
CARCINOMA, HEPATOCELLULAR, MALIGNANT, PRIMARY, METASTASIS OR NO METASTASIS:	11	5	14	12	**	2	8	6	5
CARCINOMA AND/OR HEPATOBLASTOMA	11	7	19	15					
ADENOMA/CARCINOMA AND/OR HEPATOBLASTOMA	32	36	45*	43*T		0	0	0	0
ADENOMA AND/OR CARCINOMA	0	0	0	0		14	21	18	21

continued

TABLE 46 continued
ORTHO-PHENYLPHENOL: TWO-YEAR DIETARY CHRONIC TOXICITY/ONCOGENICITY STUDY IN B6C3F1 MICE
TUMOR INCIDENCE - 24 MONTHS

SEX	MALES				FEMALES			
DOSE IN MG/KG/DAY	0	250	500	1000	0	250	500	1000
NUMBER OF MICE EXAMINED	50	50	50	50	48	50	50	50
LIVER continued								
HEMANGIOMA, BENIGN, PRIMARY:	0	3	0	2	1	1	1	0
HEMANGIOMA, BENIGN, PRIMARY: (TWO)	1	1	0	0	0	0	0	0
HEMANGIOMA, BENIGN, PRIMARY:	1	4	0	2 **	1	1	1	0
HEMANGIOSARCOMA, MALIGNANT, NO METASTASIS:	1	0	0	2	0	1	0	0
HEMANGIOSARCOMA, MALIGNANT, METASTASIS:	1	1	0	0	0	0	0	0
HEMANGIOSARCOMA, MALIGNANT, PRIMARY, METASTASIS OR NO METASTASIS:	2	1	0	2 **	0	1	0	0
LIPOSARCOMA, MALIGNANT, PRIMARY, NO METASTASIS:	0	0	0	1	0	0	0	0
STROMAL CELL SARCOMA, UTERUS, MALIGNANT, SECONDARY:	0	0	0	0	0	1	0	0
HISTIOCYTIC SARCOMA, MALIGNANT PRIMARY, NO METASTASIS:	0	0	1	0	0	0	0	0
LYMPHOSARCOMA, MALIGNANT, PRIMARY, NO METASTASIS:	0	0	0	0	1	1	0	0
HEPATOBLASTOMA, MALIGNANT, PRIMARY, NO METASTASIS:	0	2	6	2	0	0	0	0
HEPATOBLASTOMA, MALIGNANT, PRIMARY, METASTASIS:	0	0	0	1	0	0	0	0
HEPATOBLASTOMA, MALIGNANT, PRIMARY, METASTASIS OR NO METASTASIS:	0	2	6	3 **	0	0	0	0
LUNGS (NO. OF TISSUES EXAMINED)	50	50	50	50	48	50	50	50
ADENOCARCINOMA, BILE DUCT(S), MALIGNANT, SECONDARY:	0	1	0	0	0	0	0	0
ADENOCARCINOMA, BRONCHIOLOALVEOLAR, MALIGNANT, PRIMARY, NO METASTASIS:	5	1	0	1	2	2	0	0
ADENOCARCINOMA, BRONCHIOLOALVEOLAR, MALIGNANT, PRIMARY, METASTASIS:	1	1	0	0	0	0	0	0
ADENOCARCINOMA, BRONCHIOLOALVEOLAR, MALIGNANT, PRIMARY, METASTASIS OR NO METASTASIS:	6	2	0*	1T **	2	2	0	0
ADENOCARCINOMA, MAMMARY GLAND, MALIGNANT, SECONDARY:	0	0	0	0	0	0	0	1
ADENOMA, BRONCHIOLOALVEOLAR, BENIGN, PRIMARY:	10	10	11	8	5	6	4	6
ADENOMA, BRONCHIOLOALVEOLAR, BENIGN, PRIMARY: (TWO)	3	3	1	2	0	0	0	0
ADENOMA, BRONCHIOLOALVEOLAR, BENIGN, PRIMARY: (THREE)	0	0	0	1	0	0	0	0
ADENOMA, BRONCHIOLOALVEOLAR, BENIGN, PRIMARY: (FOUR)	1	0	0	0	0	0	0	0
ADENOMA, BRONCHIOLOALVEOLAR, BENIGN, PRIMARY:	14	13	12	11 **	5	6	4	6
ADENOMA AND/OR ADENOCARCINOMA, BRONCHIOLOALVEOLAR	18	14	12	12	7	8	4	6
CARCINOMA, HEPATOCELLULAR, MALIGNANT, SECONDARY:	2	2	10	4	1	2	2	2
PHEOCHROMOCYTOMA, ADRENAL MEDULLA, MALIGNANT, SECONDARY:	0	0	0	1	0	0	0	0
FIBROSARCOMA, SKIN, MALIGNANT, SECONDARY:	0	0	0	0	0	0	1	0
OSTEOGENIC SARCOMA, RIB, MALIGNANT, SECONDARY:	0	0	0	0	0	1	0	0
HEPATOBLASTOMA, LIVER, MALIGNANT, SECONDARY:	0	0	0	1	0	0	0	0
LYMPH NODE - MEDIASTINAL (NO. OF TISSUES EXAMINED)	50	10	13	49	48	20	20	49
FIBROSARCOMA, SKIN, MALIGNANT, SECONDARY:	0	0	0	0	0	1	0	0 cont'

TABLE 46 continued
ORTHO-PHENYLPHENOL: TWO-YEAR DIETARY CHRONIC TOXICITY/ONCOGENICITY STUDY IN B6C3F1 MICE
TUMOR INCIDENCE - 24 MONTHS

SEX	MALES				FEMALES			
DOSE IN MG/KG/DAY	0	250	500	1000	0	250	500	1000
NUMBER OF MICE EXAMINED	50	50	50	50	48	50	50	50
LYMPH NODE - MESENTERIC (NO. OF TISSUES EXAMINED)	50	12	13	49	48	21	22	49
HISTIOCYTIC SARCOMA, MALIGNANT, PRIMARY, NO METASTASIS:	1	0	1	0	0	0	0	0
LYMPHOSARCOMA, MALIGNANT, PRIMARY, NO METASTASIS:	0	1	0	0	0	2	0	1
LYMPH NODE - MISCELLANEOUS (NO. OF TISSUES EXAMINED)	0	2	1	0	0	1	2	0
FIBROSARCOMA, SKIN, MALIGNANT, SECONDARY:		0	0			0	1	
MAMMARY GLAND (NO. OF TISSUES EXAMINED)	1	2	2	9	28	20	22	46
ADENOCARCINOMA, MALIGNANT, PRIMARY, NO METASTASIS:	0	0	0	0	1	0	0	0
ADENOCARCINOMA, MALIGNANT, PRIMARY, METASTASIS:	0	0	0	0	0	0	0	1
ADENOCARCINOMA, MALIGNANT, PRIMARY, METASTASIS OR NO METASTASIS:	0	0	0	0 **	1	0	0	1
ADENOMA, BENIGN, PRIMARY:	0	0	0	0	1	0	0	0
ADENOMA AND/OR ADENOCARCINOMA	0	0	0	0	2	0	0	1
FIBROSARCOMA, MALIGNANT, PRIMARY, NO METASTASIS:	0	0	0	0	0	1	0	0
MEDIASTINAL TISSUES (NO. OF TISSUES EXAMINED)	50	10	13	50	48	20	22	50
ADENOCARCINOMA, BILE DUCT(S), MALIGNANT, SECONDARY:	0	1	0	0	0	0	0	0
CARCINOMA, HEPATOCELLULAR, MALIGNANT, SECONDARY:	0	0	0	1	0	0	0	0
FIBROSARCOMA, SKIN MALIGNANT, SECONDARY:	0	0	0	0	0	0	1	0
OSTEOGENIC SARCOMA RIB, MALIGNANT, SECONDARY:	0	0	0	0	0	1	0	0
MESENTERIC TISSUES (NO. OF TISSUES EXAMINED)	50	10	12	49	48	20	22	50
FIBROSARCOMA, SKIN, MALIGNANT, SECONDARY:	0	0	0	0	0	1	0	0
MULTIPLE ORGANS (NO. OF TISSUES EXAMINED)	2	5	4	2	19	16	18	12
HEMANGIOSARCOMA, MALIGNANT, PRIMARY:	0	2	1	1	0	2	1	1
OSTEOGENIC SARCOMA, MALIGNANT, PRIMARY:	0	0	0	0	0	0	1	0
HISTIOCYTIC SARCOMA, MALIGNANT, PRIMARY:	0	2	1	0	1	1	4	0
LYMPHOSARCOMA, MALIGNANT, PRIMARY:	2	1	2	1	18	13	12	11
OVARIES (NO. OF TISSUES EXAMINED)					48	26	29	50
ADENOMA, BENIGN, PRIMARY:					0	0	0	1
CYSTADENOMA BENIGN, PRIMARY:					0	1	1	0
ADENOMA AND/OR CYSTADENOMA					0	1	1	0
HEMANGIOMA, BENIGN, PRIMARY:					0	0	0	1

continued

TABLE 46 continued
ORTHO-PHENYLPHENOL: TWO-YEAR DIETARY CHRONIC TOXICITY/ONCOGENICITY STUDY IN B6C3F1 MICE
TUMOR INCIDENCE - 24 MONTHS

SEX	MALES				FEMALES			
DOSE IN MG/KG/DAY	0	250	500	1000	0	250	500	1000
NUMBER OF MICE EXAMINED	50	50	50	50	48	50	50	50
PARATHYROID GLANDS (NO. OF TISSUES EXAMINED)	48	10	11	47	43	19	20	48
ADENOMA, BENIGN, PRIMARY:	0	0	0	0	1	0	0	0
PITUITARY (NO. OF TISSUES EXAMINED)	47	10	10	40	44	18	22	43
ADENOMA, ANTERIOR (PARS DISTALIS), BENIGN, PRIMARY:	0	0	0	1	6	0	1	4
ADENOMA, PARS INTERMEDIA, BENIGN, PRIMARY:	0	0	0	0	0	0	0	1
SEMINAL VESICLES (NO. OF TISSUES EXAMINED)	50	10	13	50				
HEPATOBLASTOMA, LIVER, MALIGNANT, SECONDARY:	0	0	0	1				
SKIN AND SUBCUTIS (NO. OF TISSUES EXAMINED)	50	10	13	50	48	20	22	50
TRICHOEPITHELIOMA, BENIGN, PRIMARY:	1	0	0	0	0	0	0	0
FIBROSARCOMA, MALIGNANT, PRIMARY, NO METASTASIS:	0	0	0	1	0	1	1	2
FIBROSARCOMA MALIGNANT, PRIMARY, METASTASIS:	0	0	0	0	0	1	1	0
FIBROSARCOMA MALIGNANT, PRIMARY, METASTASIS OR NO METASTASIS:	0	0	0	1 **	0	2	2	2
SPLEEN (NO. OF TISSUES EXAMINED)	50	15	13	50	48	23	25	50
HEMANGIOSARCOMA, MALIGNANT, PRIMARY, NO METASTASIS:	1	4	1	0	1	2	1	2
LYMPHOSARCOMA, MALIGNANT, PRIMARY, NO METASTASIS:	0	1	1	0	1	0	0	0
THYMUS (NO. OF TISSUES EXAMINED)	45	9	9	45	43	18	16	40
LYMPHOSARCOMA, MALIGNANT, PRIMARY, NO METASTASIS:	1	0	0	0	0	0	0	0
THYROID GLAND (NO. OF TISSUES EXAMINED)	50	10	12	50	48	20	22	49
ADENOMA, FOLLICLE(S), BENIGN, PRIMARY:	2	0	0	0	0	0	0	1
UTERUS (NO. OF TISSUES EXAMINED)					48	29	27	50
ENDOMETRIAL STROMAL POLYP, BENIGN, PRIMARY:					2	0	1	1
HEMANGIOMA, BENIGN, PRIMARY:					0	1	0	1
HEMANGIOSARCOMA, MALIGNANT, PRIMARY, NO METASTASIS:					1	0	0	0
LEIOMYOMA, BENIGN, PRIMARY:					0	0	0	1
LEIOMYOSARCOMA, MALIGNANT, PRIMARY, NO METASTASIS:					1	1	0	0
STROMAL CELL SARCOMA, MALIGNANT, PRIMARY, METASTASIS:					0	1	0	0
UNDIFFERENTIATED SARCOMA, MALIGNANT, PRIMARY, NO METASTASIS:					0	0	0	1

continued

TABLE 46 continued
ORTHO-PHENYLPHENOL: TWO-YEAR DIETARY CHRONIC TOXICITY/ONCOGENICITY STUDY IN B6C3F1 MICE
TUMOR INCIDENCE - 24 MONTHS

SEX	MALES				FEMALES			
DOSE IN MG/KG/DAY	0	250	500	1000	0	250	500	1000
NUMBER OF MICE EXAMINED	50	50	50	50	48	50	50	50
VAGINA (NO. OF TISSUES EXAMINED)					48	20	22	50
SQUAMOUS CELL CARCINOMA, MALIGNANT, PRIMARY, NO METASTASIS:					0	0	0	1
LIPOSARCOMA, MALIGNANT, PRIMARY, NO METASTASIS:					0	0	0	1
COMBINED NEOPLASMS (TOTAL NUMBER OF ANIMALS EXAMINED)								
HISTIOCYTIC SARCOMA, ANY SITE:	1	2	3	0	1	1	4	0
LYMPHOSARCOMA, ANY SITE:	3	4	3	1	20	16	12	12
VASCULAR ENDOTHELIUM-HEMANGIOMA AND/OR HEMANGIOSARCOMA, ANY SITE:	5	11	2	5	3	7	3	5

@ DATA ARE THE NUMBER OF ANIMALS WITH THE SPECIFIED OBSERVATION.
@ POSITIVE OBSERVATIONS TABULATED, ALL OTHER TISSUES WERE WITHIN NORMAL LIMITS.
** THIS LINE REPRESENTS THE COMBINATION OF TWO OR MORE PRECEDING LINES WITH SIMILAR OBSERVATIONS AND LOCATORS.
* STATISTICALLY IDENTIFIED DIFFERENCE FROM CONTROL MEAN BY YATE'S CHI-SQUARE PAIRWISE TEST, ALPHA = 0.10, TWOALPHA = 0.05, ONE-SIDED.
T LINEAR TREND BY COCHRAN-ARMITAGE LINEAR TREND TEST, ALPHA = 0.02, TWO-SIDED, ALPHA = 0.01, ONE-SIDED.

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Chemical:	**o-Phenylphenol; Sodium o-phenylphenate**
PC Code:	**064103; 064104**
HED File Code	**13000 Tox Reviews**
Memo Date:	**12/13/95**
File ID:	**TX011737**
Accession Number:	**412-02-0011**

HED Records Reference Center
02/12/2002